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A5B BJA B180 B23Y B232 B30X B30Y B303 B35Y B351 B352 B42Y B421 B422 B44Y B441 B442 B461 B462 B48Y B480 B482 B483 B55Y B551 B57Y B58Y B585 B586 B60Y B606 B61Y B616 B64Y B644 B65Y B650 U1S S2415

(56) Documents Cited
EP 0684042 A EP 0606742 A EP 0526862 A
EP 0465265 A EP 0459632 A EP 0295637 A
US 4885314 A
Chem. Abs. 119:16776 & JP 05194209 A (Grelan Pharm. Co.) Beitr. Infusionsther. Klin. Ernaehr. - Forsch. Prax. (1983), 12(Pflanzenfasern), pages 40-7

(58) Field of Search
ONLINE: CAS-ONLINE, EDOC, JAPIO, WPI

(54) Abstract Title
Cholesterol-lowering agents

(57) A composition comprising
a) a HMG CoA reductase inhibitor, and
b) a bile complexing agent.
for the reduction of cholesterol in plasma.

The inhibitor is preferably a station or fibrate. The complexing agent is preferably fibrous and selected from biopolymers and starches.

Exemplified are compositions containing
(a) fluvastatin and isphaghula husk;
(b) fenofibrate and polyacrylic acid carbomer;
(c) pravastatin and isphaghula husk.



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# ORGANIC COMPOSITIONS

The invention relates to materials for treating patients so as to reduce the level of cholesterol in plasma, in particular to compositions for reducing cholesterol in plasma.

Raised plasma cholesterol can be a factor which contributes to coronary heart disease. Lipoproteins, especially low density lipoproteins, contribute to the transportation of cholesterol to body tissues where it can be deposited. Deposition of cholesterol can lead to the formation of plaques in arteries, resulting in turn in reduced flow of blood.

We have found a composition that ultimately leads to reduction in plasma low density lipoprotein and cholesterol levels. This is achieved by inhibiting *de novo* cholesterol synthesis in the liver and at the same time complexing bile (which is synthesised from cholesterol) in the GI tract to prevent its re-absorption. This combined activity stimulates hepatic uptake of cholesterol from the plasma, because it is required to replace the unreadsorbed bile in the absence of *de novo* synthesised cholesterol.

According to the invention, there is provided a composition comprising

a) a HMG CoA reductase inhibitor (hereinafter the Inhibitor); and

b) a bile complexing agent.

HMG CoA reductase inhibitors inhibit the activity of HMG CoA reductase, which is the committed enzyme in cholesterol synthesis, mainly in the liver.

The bile complexing agent is a compound (or compounds) that is such that when administered into a mammalian gastrointestinal tract, it will inhibit at least in part re-absorption of the said bile, by complexing with the bile so that it cannot be re-absorbed.

Further according to the invention there is provided the use of a HMG CoA reductase inhibitor for the preparation of a medicament for co-administration with a bile complexing agent for reduction of cholesterol in plasma.

Further according to the invention there is provided the use of a bile complexing agent for the preparation of a medicament for co-administration with a HMG CoA reductase inhibitor, for the reduction of cholesterol in plasma.

Further according to the invention, there is provided the use of a bile complexing agent and a HMG CoA reductase inhibitor for the preparation of a medicament for the reduction of cholesterol in plasma.

The compositions of the present invention promote hepatic uptake of plasma cholesterol and by inhibition of the re-absorption of bile reduce the level of low density lipoprotein and cholesterol circulating in blood plasma. This can lead to reduced levels of plasma cholesterol and, significantly, to reduced chance of coronary heart disease.

The compositions according to the invention can be administered as a component of a pharmaceutical composition, together with a pharmaceutically acceptable carrier.

Further according to the invention there is provided a pharmaceutical composition comprising

a) a HMG CoA reductase inhibitor (hereinafter defined as the Inhibitor),

b) a bile complexing agent, and

c) a pharmaceutically acceptable carrier.

The pharmaceutical composition can be prepared as a powder which can be administered, for example in solution or in a suspension, generally in water or an aqueous solution, for example in a dilute ethanol solution or in a drink. When administered in a solution in this way, the amount of the liquid in a single dose might be in the range from about 100 ml to about 250 ml. A composition containing the blend can be prepared as a tablet to be swallowed whole or chewed, or to be dissolved in water or other solvent.

Pharmaceutically acceptable carriers will be apparent to any man skilled in the art. They include excipients, such as flavourings, thickening agents, colouring components, preservatives etc.

Preferred Inhibitors are statins or fibrates.

Preferred statins are

fluvastatin,

pravastatin,
simvastatin.

Preferred fibrates are

clofibrate,
gemfibrozil,
ciprofibrate,
bezafibrate and
fenofibrate.

Preferably the bile complexing agents will often be essentially fibrous in nature. Suitable bile complexing agents will often contain one or more of plant cell wall materials, non-starch polysaccharides and starches. It might include other polymers, especially biopolymers. It can include other components such as thickening agents.

More preferably the bile complexing agent is selected from:

polymers of acrylic acid and its derivatives (eg carbomer),
alginic acids,
starch (resistant starch),
ispaghula husk and its fractions,
cellulosic polysaccharides and their derivatives,
guar gum,
konjak gum,
pectins and

mixtures thereof.

Preferred mixtures of the above are selected from blends of polymeric acrylic acid and alginate;

ispaghula husk with polymers of acrylic acid and their derivatives and/or guar gum; hydroxymethyl cellulose and guar gum and pectin.

Preferably the compositions are in unit dose form.

Preferably the Inhibitor is present in an amount of 0.1 to 25%, more preferably 0.15 to 20%, most preferably 0.2 to 15% by weight based on the total composition.

Preferably, the bile complexing agent is present in an amount of 1 to 60%, more preferably 2 to 55%, most preferably 5 to 50% by weight based on the total composition.

Preferably, the ratio by weight of the Inhibitor to the bile complexing agent is between 1:600 and 25:1.

The compositions according to the invention can further include other components such as flavourings, thickening agents, colouring components, preservatives etc.

The invention will now be illustrated by the following Examples.

**Example 1**

A powder formulation containing (per unit dose)

| | |
|---|---|
| Fluvastatin (commercially available) | 20 mg |
| Ispaghula husk | 3.5g |
| Sodium hydrogen carbonate | 0.5g |
| Citric acid | 3.5g |
| Flavouring agent | 0.2g |
| Colouring agent | 0.05g |

is made up as follows.

The fluvastatin and the ispaghula husk are granulated with water at room temperature. This is then dried after granulation and then dry blended with the remaining dry components.

This powder can be administered in aqueous solution after mixing at room temperature with 200 ml of water with stirring. Alternatively, the powder can be administered directly as a powder, for example being supplied in bulk with an appropriate volume measuring scoop.

**Example 2**

A liquid drink containing (per unit dose)

| | |
|---|---|
| Fenofibrate | 0.1g |
| Polyacrylic acid carbomer | |
| Carbopol 974P | 0.5g |
| Citric acid | 0.5g |
| Flavouring agents | 0.2g |
| Colouring agents | 0.05g |
| Sweetening agent | 0.05g |

is made up as follows:

The fenofibrate and the carbomer are rapidly mixed over 5 minutes. Then the citric acid is added, followed by flavouring, colouring and sweetener agent. The resulting mixture is made up by the addition of cold water to 200 mls.

The drink can be supplied in individual portion packages, for example in glass or plastic bottles or other containers such as those formed from treated paper-based materials. The drink can be supplied in larger containers from which individual doses can be measured out, for example by volume.

**Example 3**

A dispersible tablet containing

| | |
|---|---|
| Pravastatin | 20g |
| Ispaghula husk | 20g |
| Citric acid | 0.1g |
| Sodium hydrogen carbonate | 0.2g |
| Flavouring agents | 0.2g |
| Colouring agents | 0.05g |
| Tableting excipients | 0.05g |

is made up as follows:

The pravastatin and ispaghula are granulated with water at 25°C and dried. This granulated mixture is dry blended with the remaining ingredients at room temperature and tableted by conventional means.

**CLAIMS:**

1. A composition comprising

a) a HMG CoA reductase inhibitor , and

b) a bile complexing agent.

2. A pharmaceutical composition comprising

a) a HMG CoA reductase inhibitor,

b) a bile complexing agent, and

c) a pharmaceutically acceptable carrier.

3. A composition according to Claim 1 or Claim 2 in which the HMG CoA reductase inhibitor may be selected from:

Bezafibrate,
Clofibrate,
Gemfibrozil,
Fenofibrate,
Ciprofibrate,
Fluvastatin,
Pravastatin and
Simvastatin.

4. A composition according to any one of the preceding claims, in which the bile complexing agent may be selected from:

Polymers of acrylic acid and its derivatives,
Alginic acids,
Starch (resistant starch),
Ispaghula husk and its fractions,
Cellulosic polysaccharides and their derivatives,
Guar gum,
Konjak gum and
Pectins.

5. A composition containing an HMG CoA reductase inhibitor and a bile complexing agent, substantially as herein described with reference to any one of the Examples.

6. The use of HMG CoA reductase inhibitor in the preparation of a medicament for co-administration with a bile complexing agent for reduction of cholesterol in plasma.

7. The use of a bile complexing agent for the preparation of a medicament for co-administration with a HMG CoA reductase inhibitor, for the reduction of cholesterol in plasma.

8. The use of a bile complexing agent and a HMG CoA reductase inhibitor for the preparation of a medicament for the reduction of cholesterol in plasma.

9. The use according any one of Claims 6 to 8 in which the HMG CoA reductase inhibitor is selected from:

Bezafibrate,
Clofibrate,
Gemfibrozil,
Fenofibrate,
Ciprofibrate,
Fluvastatin,
Pravastatin and
Simvastatin.

10. The use according any one of Claims 6 to 9, in which the bile complexing agent is selected from:

Polymers of acrylic acid and its derivatives,
Alginic acids,
Starch (resistant starch),
Ispaghula husk and its fractions,
Cellulosic polysaccharides and their derivatives,
Guar gum,
Konjak gum and
Pectins.

11. The use of HMG CoA reductase inhibitor and bile complexing agent substantially as herein described with reference to any one of the Examples.

The Patent Office

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| **Application No:** | GB 9719754.5 | **Examiner:** | Diane Davies |
| **Claims searched:** | 1-11 | **Date of search:** | 2 February 1998 |

## Patents Act 1977
## Search Report under Section 17

**Databases searched:**

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P):

Int Cl (Ed.6):

Other: Online: CAS-ONLINE, EDOC, JAPIO, WPI

**Documents considered to be relevant:**

| Category | Identity of document and relevant passage | | Relevant to claims |
|---|---|---|---|
| X | EP 0684042 A | (EGIS Gyog.) Whole document: compositions containing gemfibrozil together with starch and hydroxypropyl methylcellulose. | At least claim 1 |
| X | EP 0606742 A | (Rohm & Haas Co.) Composition for lowering plasma cholesterol levels comprising a new bile acid sequestrant and an HMG-CoA reductase inhibitor. | 1-11 |
| X | EP 0526862 A | (Vectorpharma Int. SpA) Whole document: compositions containing cellulose ethers or acrylate polymers and an HMG-CoA reductase inhibitor. | At least claim 1 |
| X | EP 0465265 A | (Rohm & Haas Co.) Mevinic acid HMG-CoA reductase inhibitor together with a bile acid sequestrant. | 1-11 |

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|---|---|---|---|
| X | Document indicating lack of novelty or inventive step | A | Document indicating technological background and/or state of the art. |
| Y | Document indicating lack of inventive step if combined with one or more other documents of same category. | P | Document published on or after the declared priority date but before the filing date of this invention. |
| & | Member of the same patent family | E | Patent document published on or after, but with priority date earlier than, the filing date of this application. |

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**Application No:** GB 9719754.5 **Examiner:** Diane Davies
**Claims searched:** 1-11 **Date of search:** 2 February 1998

| Category | Identity of document and relevant passage | Relevant to claims |
|---|---|---|
| X | EP 0459632 A (Squibb & Sons Inc.) Whole document: composition for treating hypercholesterolaemia comprising a polyacrylamide bile acid sequestrant and an HMG-CoA reductase inhibitor. | 1-11 |
| X | EP 0295637 A (Warner Lambert Co.) Whole document: gemfibrozil, clofibrate, benzafibrate or fenofibrate together with starch and hydroxypropyl cellulose. | At least claim 1 |
| X | US 4885314 A (Merck & Co. Inc.) Mevinolin HMG-CoA reductase inhibitors administered with a bile acid sequestrant | 1-11 |
| X | Chem. Abs. 119:16776 & JP 05194209 A (Grelan Pharm. Co.) Compositions containing fenofibrate and starch. | At least claim 1 |
| X | Beitr. Infusionsther. Klin. Ernaehr. - Forsch. Prax. (1983), 12(Pflanzenfasern), pages 40-7 G. Neugebauer *et al*, "Interaction of guar with glibenclamide and bezafibrate" - disclosure of pharamcologically active composition containing guar gum and benzfibrate. | At least claim 1 |

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|---|---|---|---|
| X | Document indicating lack of novelty or inventive step | A | Document indicating technological background and/or state of the art. |
| Y | Document indicating lack of inventive step if combined with one or more other documents of same category. | P | Document published on or after the declared priority date but before the filing date of this invention. |
| & | Member of the same patent family | E | Patent document published on or after, but with priority date earlier than, the filing date of this application. |